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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,696	06/19/2001	Lisle W. George	481.06	4037

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QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,696	GEORGE ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,12-14 and 34-56* is/are pending in the application.

4a) Of the above claim(s) *1-4,6,12,34-48 and 51-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14,49,50,55 and 56* is/are rejected.

7)☒ Claim(s) *13 and 14* is/are objected to.

8)☒ Claim(s) *1-4,6,12-14 and 34-56* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

New claims 57-59 have been submitted.
Claims 13-14, 55-59 are under consideration, in so far as they are directed to isolated peptides, polypeptides or proteins of SEQ ID NO 2, and not cells that comprise SEQ ID NO 2 or variants thereof.
1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 12, 2006 has been entered.

Allowable Subject Matter

3. Claims 13-14 defined over the prior art of record and therefore are allowed.

Rejections/Objections Withdrawn

1. ***Claim Objections Withdrawn***: Claims13-14 objected to because of the following informalities have been amended to recite: ---An isolated peptide consisting ---- thus obviating the objection previously made of record.

2. ***Double Patenting Withdrawn:*** Claims 49-50 objected to under 37 CFR 1.75 as being a substantial duplicate of claims 13-14, has been obviated through cancellation of claims 49-50.

3. ***Claim Rejections - 35 USC § 112 Withdrawn***: Claims 55-56 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. for reciting in subparagraph e) the phrase "the fragment of (a) comprising any combination of (b), (c) or (d) has been obviated by canceling this subparagraph.

4. Rejection Withdrawn: Claims 55-56, subparagraphs f-h rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections has been obviated through amending the claims to recite the phrase "of SEQ ID NO: 2".

Response to Arguments

5. Applicant's arguments filed January 12, 2006 have been fully considered but they are not persuasive.

6. ***Claim Rejections - 35 USC § 102 Maintained***: The rejection of claims 55 (a, b, c, d) and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Gray et al (Vet. Microbiol., Vol. 43, pages 183-196, 1995, cited in Applicant's Specification at page 16, paragraph 2) is traversed on the grounds that the cytotoxin of Gray et al does not comprise a heterologous subsequence.

7. It is the position of the examiner that the M. bovis cytolysin of Gray et al was isolated from strain Epp63. This polypeptide while isolated from natural sources, is not identical to the polypeptide of T+ strain, from which SEQ ID NO 2 was isolated and amino acid sequenced. While the source, biological activity and the relative molecular weight are similar to the polypeptide produced by strain T+, no evidence has been made of record showing that the two polypeptides are 100% identical (amino acid sequence),

and therefore the cytolysin of Gray et al comprises a portion or subsequence that is not identical to SEQ ID NO 2, the subsequence being heterologous to SEQ ID NO 2.

The polypeptide of Gray et al (see Gray et al, the immunoblot showed immunoreactivity with the 110 kDa protein as well as several lower molecular weight bands, which would are fragments of the larger protein cytotoxin see page 190, paragraph 2, and Figure 2 and 3; also see page 194, paragraph 3 "use of the monoclonal antibodies may be attributed to recognition of smaller size antigenically related peptides") immunoreacted with an antibody that was produced to M. bovis cytolysin (see page 190, rabbit serum and monoclonal antibody, see Figure 3) and cross reacted with E.coli HlyA cytolysin (see section 3.2, page 190, Figure 2, and narrative).

The immunoblot showed the E.coli HlyA cytolysin to comprise conserved epitopes to M. bovis cytolysin, and to be smaller in size (98 kDa) to that the M.bovis cytolysin that was about 110 kDa. A polypeptide of 98 kDa is smaller in size than the polypeptide encoded by SEQ ID NO 2 (about 102 kDa), that therefore anticipates the polypeptides of subparagraphs b), c) and d) as now claimed.

New Grounds of Rejection

Claim Objections

8. Claim 56 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 56 depends from claim 55 and defines the polypeptide of claim 55 as being immunogenic, but claim 55 requires the claimed polypeptides to be over 200 amino acids in length (subparagraphs (e, f, and g), to be capable of stimulating an antibody production (subparagraph a), and large

enough to evidence hemolytic, cytolytic or corneotoxic biological activity which are shown in the instant Specification as being immunogenic. All of the polypeptides of claim 55 are immunogenic and claim 56 does not modify the structure or biological function of any of the polypeptides claimed in claim 55. Claim 56 is therefore not further limiting of claim 55 from which it depends.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 55(a), 56(a), 57(a) and 59(a) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

11. The claims have been amended to recite a combination of claim limitations that do not evidence original descriptive support in the instantly Specification. What is now claimed is a genus of polypeptides that will stimulate antibody production, the antibody being cross-reactive with SEQ ID NO 2. The claimed polypeptide is not SEQ ID NO 2 because the claimed polypeptide of subparagraph (a) comprises a sequence that is heterologous to SEQ ID NO 2 through the newly submitted combination of claim limitations: "where the polypeptide comprises a subsequence heterologous to the M.bovis cytotoxin polypeptide of SEQ ID NO 2." Where the subsequence is located or what the

subsequence is, is not defined in the claims relative to the overall polypeptide structure, the polypeptide size or polypeptide function, but the polypeptide must comprise an immunogenic epitope that will stimulate an immune response upon administration of the polypeptide to an animal.

12. Upon consideration of the instant Specification for a definition of the phrase "subsequence heterologous to the M. bovis cytotoxin", a specific definition could not be found because the term "subsequence" is not recited in the instant Specification and a genus of heterologous subsequences to SEQ ID No 2 does not evidence original descriptive support. The instantly claimed invention is directed to any polypeptide that comprises an epitope or sequence that will induce an antibody immunoreactive with SEQ ID NO 2 that also comprises a heterologous subsequence that is not present in SEQ ID NO 2.

No deposited monoclonal antibodies that could identify a specific conserved epitope is provided in the instant Specification, nor recited in the claims. Additionally, the heterologous subsequence is not defined by structure correlated with function.

What is now claimed is a highly variable genus of polypeptides that are not required to evidence any type of toxic activity, need not be of any specific size or biological function but need only induce an immuno-cross-reactive antibody with SEQ ID NO 2.

The instantly claimed highly variable genus of polypeptides does not evidence original descriptive support in the instant Specification that discloses SEQ ID NO 2, specific polypeptides 438-713, 590-927 and 643-927 of SEQ ID NO 2 and RTX polypeptides shown in Figure 4, but what is now claimed is not limited to the

polypeptides which evidence original descriptive support in the instant Specification. Therefore, claims 55-57 (a), and 59 (a) recite New Matter.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 58 recites the limitation "a 6xHis tag" in reference to the claimed polypeptide of claim 55. None of the polypeptides of claim 55 comprise a tag, no less a 6xHis tag; claim 58 should be amended to recite "The composition of claim 55 should recite ---- the polypeptide further comprising a-------. There is insufficient antecedent basis for the term "a 6xHis tag" in the recited limitations in claim 55.

15. Claim 59 recites the limitation "fusion polypeptide" in reference to the claimed polypeptide of claim 55. None of the polypeptides of claim 55 are fused with anything, no less defined as a fusion polypeptide; claim 59 should be amended to recite "The composition of claim 55, ---- the polypeptide further comprising a second polypeptide, wherein the polypeptide and the second polypeptide are joined to each other as a fusion polypeptide-------. There is insufficient antecedent basis for the term "fusion" in the recited limitations in claim 55.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

17. Claims 55(a) and 59 rejected under 35 U.S.C. 102(b) as being anticipated by Potter et al (US Pat. 5,594,107) in light of PG Pub 20030118566 A1 [0182].

Potter et al disclose the instantly claimed invention directed to a polypeptide (see claim 1, col. 51) that will immunoreact with an antibody produced to SEQ ID NO 2, and comprises a heterologous subsequence to M. bovis cytotoxin, the polypeptide of Potter et al being an homologous polypeptide to the RTX cytotoxin of Moraxella bovis (see Potter et al, col. 5, line 7), wherein the fragment is an amino acid sequence of SEQ ID NO 2 (see col. 5, lines 1-2), specifically Gly-Gly-X-Gly-Asn-Asp (Potter et al SEQ ID NO 5) which are amino acids 729-734 of Instant SEQ Id NO 2. PG Pub 20030118566 A1 [0182] shows anti-glycine antibodies are commercially available thus defining the Glycine in the disclosed fragment of Potter et al to be immunogenic and would specifically immunoreact with an antibody thereto, the glycine being present also in SEQ ID NO 2 of M bovis.

Additionally, the sequence of Potter comprises a heterologous amino acid sequence to SEQ ID No 2, which is claimed to include any one of the amino acids of Potter's polypeptide of claim 2 (col. 51, lines 32-33) and is also a chimeric fusion protein (see Potter claim 1 and Figure 2).

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior

art (i.e., that the protein of the prior art does not possess the same functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594

Inherently the reference anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior arts functioning, does not render the old composition patentably new to the discoverer. The Court further held that Athis same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art.

18. Claims 55(a-d) and 56are rejected under 35 U.S.C. 102(b, June 2000) as being anticipated by Billson et al.

Billson et al disclose the instantly claimed invention directed to an isolated polypeptide that evidences hemolysin (title), cytolytic (see page 3470, col. 2, p 6-7) and corneotoxic (see page 3470, col. 2, p 6-7; page 3471, col. 1, p 3-4) activity, which evidences a relative molecular weight of 94 kDa which is smaller than the polypeptide represented by SEQ ID No 2. The polypeptide was isolated from Moraxella bovis strain UQV148NF which is not the same strain T+ from which SEQ ID No 2 was isolated, and would inherently comprise a heterologous subsequence to SEQ ID NO 2. Billson et al anticipates the instantly claimed invention as now claimed.

19. Claims 55 (b-c) and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al (1990).

Please note : claim 55 (b-c) and 56 claim polypeptides of a specific biological function which must be smaller than SEQ ID NO 2 (927 amino acid) but is not required to be SEQ Id NO 2; SEQ ID No 2 defining the upper limit in the size of the polypeptide.

Yamamoto et al (1990) disclose an isolated cytolysin and hemolysin polypeptide that comprises 741 amino acids, which is shorter than SEQ ID NO 2, which is a sequence of 927 amino acids. Yamamoto et al anticipates the instantly claimed invention as now claimed, a polypeptide with cytolysin and/or hemolytic activity, is shorter than SEQ ID No 2, and is immunogenic.

20. Claims 55 (a, c), 56, 57, 58, and 59 are rejected under 35 U.S.C. 102(e) as being anticipated by Highlander et al (US Pat. 6,180,112, filing date April 1999, effective filing date April 1997).

Highlander et al disclose an isolated polypeptide that will immunoreact with an antibody produced to SEQ ID NO 2, in light of the sequence alignment provided in Applicant's instant Specification and figures which show Pasteurella haemolytic leukotoxin A (LktA) to share sequence identity with SEQ ID NO 2, and to also comprise heterologous subsequences (percent identity and homology is not 100%), wherein Highlander's polypeptide is recombinantly expressed as a fusion polypeptide (see Highlander et al :col. 14, lines 3-19 and lines 29-34), wherein the polypeptide is a full length polypeptide that comprises a heterologous subsequence (see col. 13, lines 40-54), or is

a polypeptide that is a fragment of the leukotoxin (see Highlander et a, col. 13, line 43), together with a six histidines (see col. 14, line 14 "six to ten residues"), referred to as an affinity tag (see Highlander et al, col. 14, lines 3-34), the leukotoxin evidencing hemolytic activity.

Highlander et al anticipates the instantly claimed invention as now claimed which reads on fusion polypeptides of homologous polypeptides that comprise conserved epitopes and evidence a common biological function but need to be SEQ ID NO 2, and is shorter in length than SEQ ID No 2.

Conclusion

21. This is a non-final action.

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

23. US006797272B1 US006096320A US006797272B1 US005837268A US006096320A US006475754B1 are cited to show cytotoxins (leukotoxins) compositions.

24. Hess et al (2006), Angelos et al (2003), Burrows et al (1993), Smits et al (1991) , Pellett et al (1996), Lally et al (1997) and Gerbig, Jr. Et al (1992) is cited to show leukotoxin/hemolysin polypeptide compositions..

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
April 6, 2006

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600